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Chronic diseases and social risk factors in relation to specific symptoms of depression: Evidence from the U.S. National Health and Nutrition Examination Surveys

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Abstract

Background: Depression is a heterogeneous mental disorder with multiple symptoms, but only few studies have examined whether associations of risk factors with depression are symptom-specific. We examined whether chronic diseases and social risk factors (poverty, divorce, and perceived lack of emotional support) are differently associated with somatic and cognitive/affective symptoms of depression.

Methods: Cross-sectional analyses were based on individual-level data from the 31,191 participants of six cross-sectional U.S. National Health and Nutrition Examination Surveys (NHANES) carried out between 2005 and 2016. Depressive symptoms were assessed using the 9-item Patient Health Questionnaire. Information on chronic diseases and social risk factors was self-reported by participants.

Results: After adjustment for sex, age, race/ethnicity, and all the of other symptoms besides the outcome symptom, higher number of chronic diseases was independently related to fatigue, psychomotor retardation/agitation, and sleep problems in a dose-response pattern (range of odds ratios: 1.21 to 2.59). Except for concentration problems, social risk factors were associated with almost all of the cognitive/affective symptoms (range of odds ratios: 1.02 to 2.09) but only sporadically with somatic symptoms.

Limitations: All measures were self-reported by the participants, which may have introduced bias to the associations. Cross-sectional data did not allow us to study temporal dynamics.

Conclusions: Specific symptoms of depression may be useful in characterizing the heterogeneous etiology of depression with respect to somatic versus social risk factors.

Keywords: Heterogeneity; Depressive symptoms; Disease; Network; Risk factors; Symptomics

Depression is a heterogeneous mental disorder that can involve affective, cognitive, and somatic symptoms (Fried, 2017). The assessment and diagnosis of depression is often based on the number of symptoms, without considering the specific nature of these symptoms. High depression scores can therefore represent many different symptom combinations. Various subtypes of depression have been introduced to account for its heterogeneous nature (e.g., melancholic or atypical depression) but most of these subtypes have not received strong empirical support (Foster and Mohler-Kuo, 2017; Harald and Gordon, 2012; van Loo et al., 2012). For example, it remains unclear whether specific symptoms are differently related to environmental risk factors (Fried et al., 2014; Keller et al., 2007), biomarkers (Jokela et al., 2015; Lamers et al., 2017), and genetic liabilities (Kendler et al., 2013; Kendler and Aggen, 2017). Better understanding of symptom-specific associations could contribute to a better characterization of depression heterogeneity.

One important source of heterogeneity in depression arises from the difference between somatic and cognitive/affective symptoms (van Loo et al., 2012; Lux and Kendler, 2010; Wanders et al., 2016). Somatic symptoms include fatigue, sleep problems, appetite or weight change, and psychomotor retardation or agitation. Cognitive/affective symptoms comprise of a lack of interest, sad mood, feelings of worthlessness, thoughts of death, and difficulties in concentration (van Loo et al., 2012; Lux and Kendler, 2010). Studies of depression and inflammation have suggested that inflammation—a biomarker associated with many physical illnesses—may be specifically related to somatic symptoms of depression but not with cognitive/affective symptoms (Jokela et al., 2015; Lamers et al., 2017; White et al., 2017), implying a close connection between poor physical health and somatic depressive symptoms.

There is also evidence that social risk factors might have specific associations with cognitive/affective symptoms, although the profiling remains unclear. In a longitudinal study

of bereavement, widowhood was associated with increased cognitive/affective symptoms (loneliness, sadness, and depressed mood, and decreased happiness and enjoying life) but also with loss of appetite (Fried et al., 2015). Another study found that, after adjustment for the number of symptoms, higher educational level was simultaneously associated with higher occurrence of sleep problems and fatigue but lower occurrence of psychomotor retardation/agitation and suicidal ideation (Lux and Kendler, 2010). Furthermore, different types of life events may be associated with different symptom profiles (Keller et al., 2007).

Adding to the growing number of investigations using symptom-level analysis of mental disorders (Fried et al., 2017; Guloksuz et al., 2017), we examined whether the number of chronic diseases are related to different symptoms of depression compared to three social risk factors: poverty, perceived lack of emotional support, and divorce. We hypothesized that increasing number of chronic diseases is most strongly associated with somatic symptoms of depression, and that social risk factors are specifically associated with cognitive and affective symptoms but not with somatic symptoms. We did not have specific hypotheses about differences among the somatic, or among the cognitive and affective, symptoms. However, instead of creating summary scores of somatic and cognitive/affective dimensions, we examined the symptoms individually to see whether the differences were observed systematically across all somatic vs cognitive/affective symptoms.

Methods

Participants

Participants were from the National Health and Nutrition Examination Surveys (NHANES, https://www.cdc.gov/nchs/nhanes/index.htm) of 2005-2006 (n=4,799), 2007-2008 (n=5,415), 2009-2010 (n=5,546), 2011-2012 (n=4,925), 2013-2014 (n=5,372), and 2015-2016 (n=5,134) with a total of 31,191 adult participants aged at least 18 years (Center for Disease Control,

2018). The NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States steered by the National Center for Health Statistics, which is part of the Centers for Disease Control and Prevention. In 1999, the NHANES became a continuous program that has a changing focus on a variety of health and nutrition measurements. The survey examines a nationally representative sample of about 5,000 persons annually. These people are located in counties across the country, 15 of which are visited each year. The samples are selected to represent the U.S. population of all ages. Persons aged 60 and older, African Americans, and Hispanics were over-sampled to produce reliable statistics. Health interviews are conducted in respondents' homes. Depressive symptoms, but not all the covariates, have been assessed from all the adult NHANES participants since the 2005-2006 data collection, so the analytic sample varied in size depending on the covariates included in the analysis. The mean age of the participants was 47.5 years (SD=18.8). Twenty four percent of the participants had a college degree, 30% some education beyond high school, 22% had completed high school, and 23% had less education than high school. The symptom-specific age patterns of depression have been previously described in the NHANES cohorts (García-Velázquez et al., 2019).

Measures

Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-9) as part of computer-assisted personal interviews (Kroenke et al., 2001). The nine items of the questionnaire query how often the participant had been bothered by specific depression symptoms during the last 2 weeks, each self-rated on a 4-point response scale (0=Not at all, 1=Several days, 2=More than half the days, 3=Nearly every day). The number of *chronic diseases* was determined as the sum of six self-reported diseases (coronary heart disease, stroke, respiratory disease, diabetes, cancer, and arthritis) with the sum score being top-coded

to three or more diseases. In the current study, we were not interested in potential differences between specific diseases. Rather, we used the number of chronic diseases as a measure of overall physical health because we assumed that reporting chronic disease diagnoses is less likely to be influenced by depressive symptoms than self-reported measures of general physical health. *Perceived lack of emotional support* was measured with the question "In the last 12 months, could you have used more emotional support than you received?" with response options "Yes" and "No". Information on this variable was collected only in 2005-2006 and 2007-2008, and only from participants aged 40 or older. *Divorce* was assessed based on marital status reported by the participants. Only married and divorced individuals were included in the analysis of divorce and depression symptoms. *Poverty* was determined on the basis of the family's monthly poverty level index, which is calculated by dividing family income by poverty guidelines defined by the U.S. Department of Health and Human Services (https://aspe.hhs.gov/poverty-guidelines). The poverty index is specific to family size, year, and state, and it is used to determine families' financial eligibility for certain federal programs, such as the Head Start and the National School Lunch Program. We used poverty- index ratio as a categorical variable with poverty being determined as the household's income being below the poverty line, that is, poverty index ratio < 1. These three social risk factors were selected because they were available across more than one study year; the NHANES surveys do not collect data on adverse life events or stressful life circumstances that would have been useful for our analysis. *Race/ethnicity* was reported by the participants and recoded into 4 categories (0=non-Hispanic white, 1=non-Hispanic black, 2=Mexican American or other Hispanic, 3=Other).

Statistical analysis

Ordered logistic regression (i.e., proportional odds model) was used to examine the associations of risk factors with individual depression symptoms. Given that all symptoms of depression are correlated with each other, it is important to examine symptom-specific associations when the associations of other symptoms are partialled out. We therefore adjusted all the analyses for all the other eight symptoms besides the symptom used as the outcome variable. All the associations were further adjusted for age, sex, race/ethnicity. The models were first fitted in each study separately and then the study-specific estimates were pooled together using meta-analysis with inverse variance method (i.e., two-step meta-analysis). We used fixed-effect meta-analysis because all the NHANES samples are based on the same source population and sampling scheme. Sampling weights were used in all analyses to take into account the complex survey design. Statistical analysis was performed with Stata 15.0. (StataCorp, College Station, Texas).

Results

Table 1 shows the descriptive statistics of the samples. Adjusted for sex, age, and race/ethnicity, poverty correlated with divorce status (partial correlation r=0.13), lack of emotional support (0.09), and number of chronic diseases (0.08), the latter two also correlating with divorce status (0.07 and 0.05, respectively) and with each other (0.04). The associations of chronic disease count and depressive symptoms are shown in **Figure 1**. There was a monotonic dose-response trend between number of chronic diseases and feeling tired and having little energy, and moving/speaking slowly (or too fast): the more chronic diseases were reported, the more severe were the symptoms. Having trouble sleeping and poor appetite (or overeating) were also elevated among those with more chronic diseases but without a monotonic dose-response trend. Sad mood (i.e., feeling down) was also related to number of chronic diseases while concentration problems were slightly elevated but without

a dose-response association. There were no clear associations with other cognitive and emotional symptoms.

The social risk factors were more systematically associated with cognitive and affective symptoms than with somatic symptoms (**Figure 2**). Compared to those who were married or living with a partner, individuals who were divorced had higher levels of anhedonia, sad mood, worthlessness, suicidal thoughts, and sleep problems but lower levels of fatigue. Poverty was related to higher levels of anhedonia, sad mood, suicidal thoughts, and movement retardation/agitation. Perceived lack of emotional support was associated with anhedonia, sad mood, worthlessness, and poor appetite (or overeating).

With 9 depressive symptoms and 4 risk factors (considering number of chronic diseases as a continuous variable to test for linear trends), we carried out 36 tests. To examine the likelihood of finding false-positive associations, we used the Benjamini–Hochberg test (Benjamini & Hochberg, 1995) to adjust the p-values for a false discovery rate of 0.10 and 0.05 (**Supplementary Table 1**). Of the 21 statistically significant associations, all would have been statistically significant when allowing for a false discovery rate of 0.10 and only 1 would not have been significant (p=0.071) when allowing for a false discovery rate of 0.05, suggesting that most of the associations were unlikely to be false discoveries. The cohort-specific associations between risk factors and depressive symptoms are shown in **Supplementary Figures S1** to **S18**.

Discussion

We examined whether two major categories of mental health risk factors—number of chronic diseases and social factors—were associated with different sets of depressive symptoms. After taking into account all the other depressive symptoms, there was a dose-response association between the number of chronic diseases and most somatic symptoms (i.e.,

fatigue, sleep problems, changes in appetite, psychomotor abnormalities) but not with cognitive and affective symptoms. Poverty, divorce, and perceived lack of emotional support, by contrast, were primarily associated with cognitive and affective symptoms (i.e., anhedonia, sad mood, worthlessness, and thoughts about death) while the associations with somatic symptoms were less consistent.

These findings support the usefulness of analysis that focuses on individual symptoms of mental disorders (Fried et al., 2014; Fried and Nesse, 2015) rather than just the sum of all symptoms; symptom-specific analysis may provide more detailed results on the heterogeneous etiology of depression. The dose-response associations between the number of chronic diseases and somatic symptoms of depression probably reflect the physical and physiological complications involved in the progression of chronic diseases (Stanton et al., 2007). Chronic diseases are not only biological conditions but also involve psychological and social difficulties (e.g., limitations in carrying out daily activities and interacting with other people), and therefore they may additionally relate to psychosocial difficulties or reflect the overall disease burden. Inflammatory markers (e.g., C-reactive protein) appear to be specifically associated with somatic but not with cognitive symptoms (Fried et al., 2018; Jokela et al., 2015; Lamers et al., 2017; White et al., 2017), although the evidence for this is not completely consistent (Gallagher et al., 2017; Köhler-Forsberg et al., 2017; Myung et al., 2016). Additional studies on symptom-specific associations of biomarkers other than inflammation (Chirinos et al., 2013) could produce additional insights into the link between physical health and depression.

Divorce, poverty, and perceived lack of emotional support were associated with increased levels of almost all cognitive and affective symptoms. Depression risk is known to increase with stressful life events, especially those representing loss (Keller et al., 2007) and social conflict (Hagen and Rosenstrom, 2016; Rosenström, 2013; Rosenström et al., 2017),

such as divorce. Poverty is accompanied by elevated psychosocial and economic strain and with fewer resources to mitigate the adverse effects of strain (Lorant et al., 2003). Similarly, social support is an important buffer that helps people to cope with difficult life events and circumstances (Haber et al., 2007). Psychosocial strain, in turn, can lead to the development of dysfunctional beliefs, such as worthlessness, hopelessness, and loss of interest for activities (Pemberton and Fuller Tyszkiewicz, 2016). This may explain why social risk factors were related specifically to cognitive and affective symptoms of depression. Obviously, social risk factors may also contribute to the development of physical illnesses, but it appears that these associations are not reflected in symptom-specific associations of depression.

Concentration problems showed no dose-response association with the number of chronic diseases nor consistent associations across the social risk factors. Some previous studies have found no independent associations of concentration problems with inflammatory markers (e.g., Jokela et al., 2016; Lamers et al., 2018) or with other risk factors (Lux & Kendler, 2010). Perhaps concentration problems are etiologically more complex and could be further divided into more fine-grained components to reveal independent associations with risk factors (Thombs et al., 2010). Indeed, concentration problems have been considered both as cognitive symptoms (e.g., van Loo et al., 2012) and somatic symptoms (e.g., Steer et al., 1999) or to be divided into cognitive and somatic clusters (Thombs et al., 2010).

Previous studies of symptom-specific associations of depression have focused particularly on how different types of life events precede the onset of depressive episode. In the Changing Lives of Older Couples study, widowhood was specifically associated with cognitive/affective symptoms of loneliness, sadness, and depressed mood but also with appetite loss (Fried et al., 2015). In the Virginia Twin Study (Keller et al., 2007), romantic losses were associated specifically with higher levels of sadness, anhedonia, and appetite

loss, and with lower levels of fatigue, agitation, hypersomnia, appetite gain, and guilt. This supports the distinction between cognitive/affective and somatic symptoms related to a social loss. On the other hand, in the same study health issues were associated with higher appetite gain but lower insomnia, guilt, fatigue, and appetite loss, which is not consistent with the hypothesis of somatic-specific associations with health. In another study with the Virginia Twin Study (Lux and Kendler, 2010), higher educational level was simultaneously associated with higher occurrence of sleep problems and fatigue but lower occurrence of psychomotor retardation/agitation and suicidal ideation, which is an unexpected pattern related to a social risk factors such as education. A study of Canadian adolescents (Harkness & Stewart, 2009) examined how cognitive/affective and somatic symptoms might differently predict subsequent life events; cognitive/affective symptoms were predictive of interpersonal life events that were dependent on the person (e.g., argument with a friend) while somatic symptoms were predictive of life events that were not dependent on the person (e.g., health issues of family members).

Our study has methodological strengths, such as the large sample size of the six NHANES studies which yielded regression coefficients estimated with little measurement imprecision. Furthermore, although a short screening instrument, the Patient Health Questionnaire does cover all the DSM-5 symptoms of depression. However, the current results also need to be considered with at least four limitations. First, the study was based on a population-based sample, and the symptom-specific associations might not be similar in clinical samples of depressed individuals (Foster and Mohler-Kuo, 2017). Second, depressive symptoms were assessed with a short self-reported rating scale, and the results might be different with clinical interviews or with other rating scales of depression, as different measures may provide more or less accurate tools to differentiate between specific symptoms (Fried, 2017). In particular, it would be useful to have multiple questions for each symptom

to improve measurement reliability. Also, separate items would be required to assess typical vs atypical compound symptoms of weight gain vs loss, trouble of sleeping vs sleeping too much, and psychomotor retardation vs agitation (Lamers et al., 2017), which was not possible the PHQ-9 scale used in our current study.

Third, our analyses were limited to six chronic diseases and three social risk factors because the data did not include many other potential risk factors of depression, such as life events. Future studies need to examine a broader scope of biological, psychological, and social risk factors to establish the robustness of symptom-specific patterns. The measure for lack of emotional support was based on the participant's self-perceived need for more emotional support and not on objectively available emotional support or social support more generally. Studies of social support do, however, suggest that self-perceived support is an important predictor of mental and physical health, even above actually received support (Haber et al., 2007; Hakulinen et al., 2016). Fourth, the data were cross-sectional so we could not determine the temporal order between chronic diseases, social risk factors, and depressive symptoms; it is possible that specific symptoms contribute differentially to disease progression and life outcomes such as divorce and poverty risk (Harkness and Stewart, 2009).

Symptom-specific associations may help to delineate more homogeneous subsyndromes of depression and to identify specific developmental pathways leading to depression. It is plausible that different risk factors lead to different symptom trajectories, and that these trajectories differ in their stability, severity, and the strength with which specific symptoms influence each other (cf. Bringmann et al., 2015). Such information would be valuable in evaluating the etiology and prognosis of depressive states. For example, if the cognitive and emotional symptoms are primarily related to social risk factors, then a high score on these dimensions in comparison to somatic symptoms might suggest specific hypotheses about the origins of a person's depression. The prognosis might also be different

for different symptom constellations. However, additional studies with longitudinal data and broader set of risk factors are needed to test these hypotheses further.

In conclusion, our results suggest that higher number of chronic diseases is independently associated with somatic symptoms while social risk factors are independently associated with cognitive and affective symptoms of depression. These patterns suggest that symptom-level analysis of different types of risk factors can be used to better reduce the heterogeneity of depression by identifying more specific structures and dynamics of depressive states.

Table 1. Frequencies of study variables and their associations with depression sum score in the six National Health and Nutrition Examination Surveys (NHANES) cohorts (n=31,191)

	Numbers (percentages)	B (95% CI) *
Sex		
Male	15334 (49.2)	(reference)
Female	15857 (50.8)	1.05 (0.96, 1.14)
Race/ethnicity		
Non-Hispanic white	13387 (42.9)	(reference)
Non-Hispanic black	6754 (21.7)	-0.02 (-0.14, 0.11)
Hispanic	8147 (26.1)	0.13 (0.01, 0.24)
Other	2903 (9.3)	-0.48 (-0.65, -0.31)
Number of chronic diseases		
None	17132 (59)	(reference)
One	7348 (25.3)	1.47 (1.35, 1.60)
Two	3268 (11.3)	2.62 (2.44, 2.79)
Three or more	1274 (4.4)	3.93 (3.68, 4.18)
Divorce		
Not divorced	25628 (86.0)	(reference)
Divorced	4175 (14.0)	1.26 (1.12, 1.40)
Poverty		
Not poverty	22272 (77.5)	(reference)
Poverty	6462 (22.5)	1.53 (1.41, 1.65)
Perceived lack of emotional support†		
No	4405 (79.4)	(reference)
Yes	1141 (20.6)	2.39 (2.13, 2.65)

† Data collected only in NHANES 2005-2006 and 2007-2008

* Regression coefficient of the variable when predicting depression sum score, adjusted for sex, age, and race/ethnicity. The regression models were first fitted separately in each cohort and then the coefficients were pooled into a summary estimate using fixed-effect meta-analysis. CI = Confidence interval

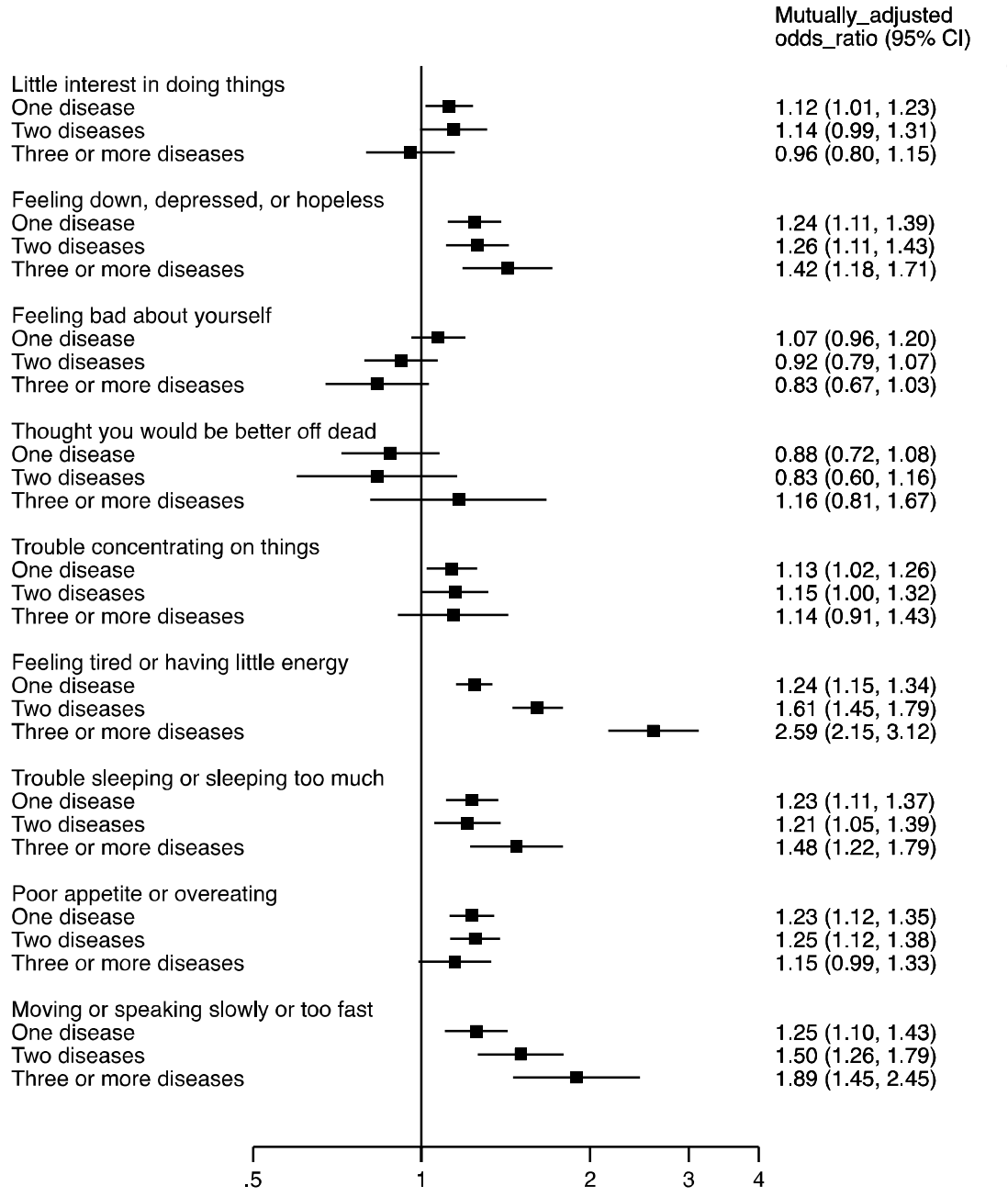

Figure 1. Associations between number of chronic diseases and individual depression symptoms. Meta-analytic odds ratios across cohort studies adjusted for age, sex, race/ethnicity, and all the other depressive symptoms. Reference category is participants with no chronic diseases.

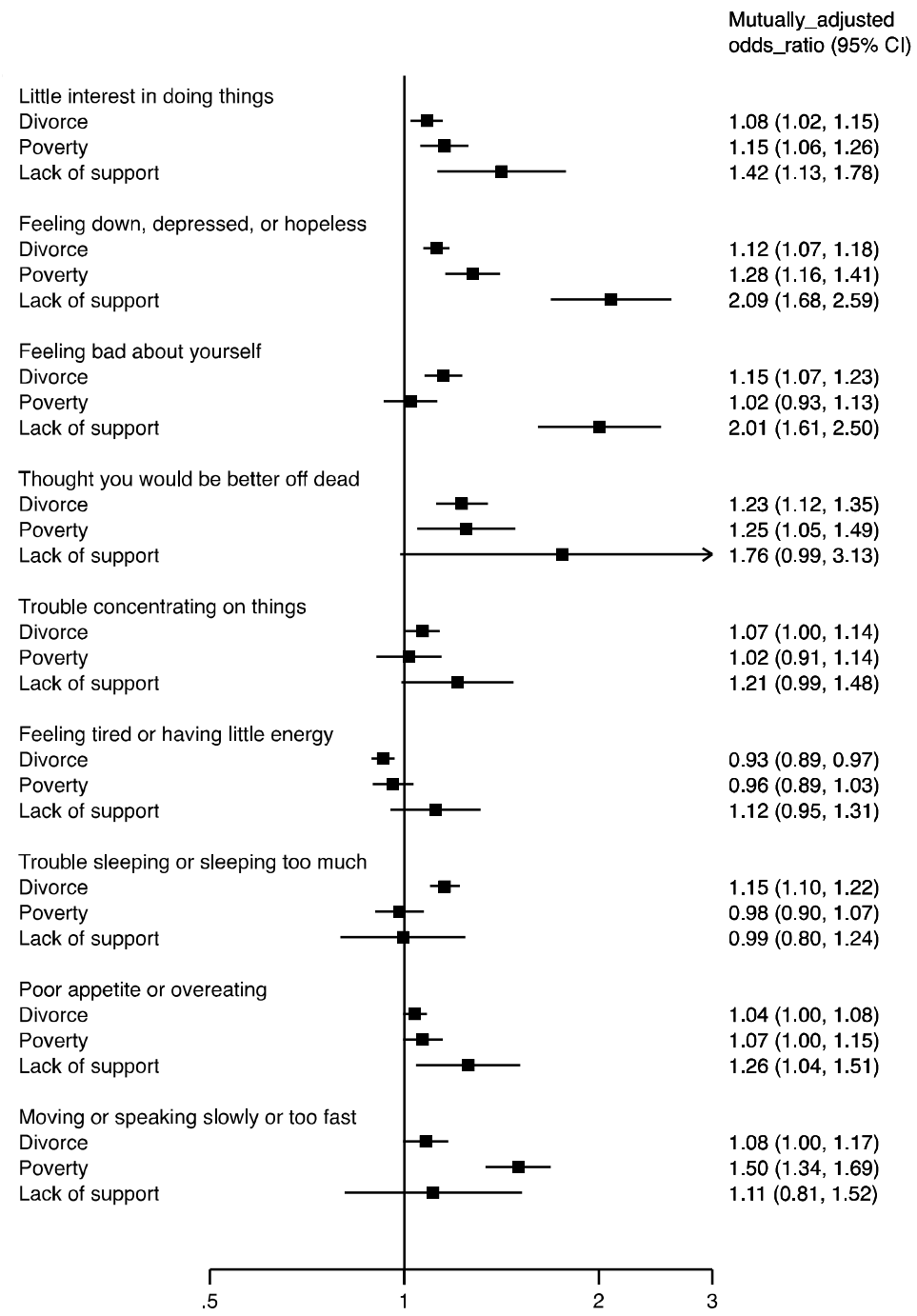

Figure 2. Associations between social risk factors and individual depression symptoms. Meta-analytic odds ratios across cohort studies adjusted for age, sex, race/ethnicity, and all the other depressive symptoms. Reference categories are married/cohabiting participants (divorce), participants above the poverty line (poverty), and those who reported having sufficient emotional support (lack of support).

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